PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 29607P WO	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2004/010582	International filing date *(day/month/year)* 21.09.2004	Priority date *(day/month/year)* 22.09.2003
International Patent Classification (IPC) or national classification and IPC A61K31/00, A61K31/56, A61K31/185, A61K31/215, A61P19/00, A61P19/10		
Applicant BIONETWORKS GMBH		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 12 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

Date of submission of the demand 19.07.2005	Date of completion of this report 31.01.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Loher, F Telephone No. +49 89 2399-7839

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/010582

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:

   ☐ international search (under Rules 12.3 and 23.1(b))
   ☐ publication of the international application (under Rule 12.4)
   ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-65 as originally filed

   Claims, Numbers

   1-15 received on 12.01.2006 with letter of 12.01.2006

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:

   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/010582

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	6-12,15
	No:	Claims	1-5,13,14
Inventive step (IS)	Yes:	Claims	8,10,11
	No:	Claims	1-7,9,12-15
Industrial applicability (IA)	Yes:	Claims	1-15
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (SEPARATE SHEET)

International application No.
PCT/EP2004/010582

Re Item I

Basis of the report

Claims 1-15 filed with letter dated 12.01.2006 have been examined.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: DE 20 50 072 A (BONATI) 20 April 1972 (1972-04-20)
D2: COOPER MARK S ET AL: "Modulation of 11beta-hydroxysteroid dehydrogenase isozymes by proinflammatory cytokines in osteoblasts: An autocrine switch from glucocorticoid inactivation to activation" JOURNAL OF BONE AND MINERAL RESEARCH, vol. 16, no. 6, June 2001 (2001-06), pages 1037-1044, XP009042532 ISSN: 0884-0431
D3: PATENT ABSTRACTS OF JAPAN vol. 1996, no. 03, 29 March 1996 (1996-03-29) & JP 07 291857 A (SUNTORY LTD), 7 November 1995 (1995-11-07)
D4: WO 02/076435 A (MORTON NICHOLAS MICHAEL ; SECKL JONATHAN ROBERT (GB); WALKER BRIAN ROB) 3 October 2002 (2002-10-03)
D5: US 3934027 A (HESS) 20 January 1976 (1976-01-20)

If not mentioned otherwise, the relevant passages are those mentioned in the international search report.
The document D5 was not cited in the international search report. A copy of the document is appended hereto.

Art 33(2) The present application does not meet the requirements of Article 33(2) PCT, since the subject-matter of claims 1-5, 13 and 14 is not new.
In interpreting claims 1-15 for determining novelty, the diseases to be treated are decisive. The discovery of a new mechanism of action even if representing an important piece of scientific knowledge, still needs to find a practical application in the form of a defined, real treatment of a pathological condition in order to make a technical contribution to the art and be considered as an invention eligible for patent protection. A new mechanism of action is only relevant with respect to novelty of a claim directed to a second medical use of a known compound or composition, in so far as this mode of action results in a new use of the known product. This new use is the technical feature which must be included in the wording of the respective claims.

In the present case, D3 discloses the use of glycyrrhetinic acid compounds (which are capable of inhibiting 11bHSD) for the treatment of malignant hypercalcemia, Paget's disease of the bone or osteoporosis. Osteoporosis is mentioned in present claim 1 and Paget's disease is a disease which falls under the definition bone erosion and/or proteoglycan damage. Malignant hypercalcemia is a specific condition which occurs in connection with bone loss by cancer and lytic bone metatstases. Therefore, the subject-matter of claims 1-5, 13 and 14 is not new in the light of D3.

Art 33(3) The present application does not meet the requirements of Article 33(3) PCT, since the subject-matter of claims 1-7, 9 and 12-15 does not seem to involve an inventive step.
D3, which is considered to represent the most relevant state of the art, discloses the use of glycyrrhetinic acid compounds for the treatment of malignant hypercalcemia, osteoporosis or Paget's disease of the bone.
The problem to be solved by the present invention may therefore be regarded as how to provide improved medicaments for the treatment of inflammation- or immune-mediated bone loss.
The present application suggests to solve the problem posed by using 11-beta

HSD inhibitors.

Taking into account the teaching of the cited prior art the following reasoning applies:

With respect to the subject-matter of claims 1-5, 13 and 14 the applicant's attention is drawn to the fact that even if novelty could be established over the above-cited prior art it is at present not clear wherein an inventive step may reside.

With respect to the subject-matter of claims 6, 7 and 9 the applicant's attention is drawn to the fact that there seems to be no basis for inventive step within the present application as filed since no evidence can be found that the features which are novel over the prior art contribute to the solution of the posed problem. As can be seen from the experimental data disclosed in the present application only the compounds represented by formulas 7, 13, 14, 16, 24 and 25 are effective 11-beta HSD inhibitors. In addition it is held that all compounds which have been demonstrated to be effective 11-beta HSD inhibitors and which have the pentacyclic core of formula I or II do have an oxo group on position 11. Bearing in mind that firstly, the C11 of the pentacyclic core interacts with the active site of the enzyme 11-beta hydroxydehydrogenase, that secondly neither formula I or II includes the C11 oxo feature and finally the application has not shown that compounds which fall within the scope of formula I or II in fact do inhibit 11-beta HSD it is held that the posed problem has not been solved by the subject-matter of the claims in question.

With respect to the subject-matter of claims 12, 13 and 15 the applicant's attention is drawn to the fact that there seems to be no basis for inventive step within the present application as filed since no evidence can be found that the features which are novel result in a solution of the posed problem which could not have been foreseen by the skilled person.
The selection of oral administration out of a list which contains all modes of administration appears to be an arbitrary selection.
To combine medicaments which are directed to the same use (as suggested by

claim 12) is a straight-forward action for the skilled person.
Since there is no surprising effect resulting from that selection or combination, the solution proposed in claims 12, 13 and 15 of the present application is not considered to be inventive in the sense of Article 33(3) PCT.

The subject-matter of claims 8, 10 and 11 seems to involve an inventive step in the sense of Article 33(3) PCT. The contribution to the art made by the subject-matter of these claims is that the compounds defined in said claims are effective 11-beta HSD inhibitors. The present application demonstrates data which links 11-beta HSD inhibitin with inflammation- or immune-mediated bone loss which makes it reasonable that these specific compounds will be effective in the treatment of such a condition and, thus, solve the posed problem.
Therefore, the solution proposed by claims 8, 10 and 11 of the present application is considered to be inventive in the sense of Article 33(3) PCT.

Art 33(4) The subject-matter of claims 1-27 is considered to be industrially applicable in the sense of Art 33(4) PCT.

Re Item VIII

Certain observations on the international application

Position 14 of formula I is linked to a methyl group which defines C14 of formula I as a quarternary carbon atom. The option of an unsaturated bond between C13 and C14 of formula I as defined in present claim 7 is chemically not possible in view of the quarternary character of C14. This renders the subject-matter of claim 7 unclear.

Position 9 of formula II is linked to a methyl group which defines C9 of formula II as a quarternary carbon atom. The option of an unsaturated bond between C8 and C9 of formula II as defined in present claim 9 is chemically not possible in view of the quarternary character of C9. The same applies to the option of an unsaturated bond between C13 and C14. All this renders the subject-matter of claim 9 unclear.

In view of the experimental data of the present application it appears that on position 11 of both formula I and II an oxo group would be an essential structural feature of a compound which should be an alleged 11-beta HSD-1 or 11-beta HSD-2 inhibitor. Neither of both formulas defines an oxo group as substituent on position 11 of the ring systems. This renders the subject-matter for which protection is sought unclear, since the compounds which are structurally defined by formula I and II are on the same time functionally defined as 11-beta HSD inhibitors. All this renders the subject-matter of claims 7 and 9 unclear.

International Patent Application
No. PCT/EP2004/010582
BioNetWorks GmbH
29607P WO/MDmh

New Claims

1. Use of an 11-β-HSD-type 1 and/or type 2 inhibitor or a pharmaceutically acceptable salt thereof, for the manufacture of a pharmaceutical agent for the prevention and/or treatment of inflammation-induced and/or immune-mediated loss of bone and/or cartilage, wherein said use is for the prevention and/or treatment of osteoporosis, postmenopausal osteoporosis, lytic bone metastases, arthritis, juvenile chronic arthritis and/or adjuvant arthritis, infectious diseases, bone loss by cancer, bone loss by HIV, tooth loss, bone marrow inflammation, synovial inflammation, cartilage and/or bone erosion and/or proteoglycan damage.

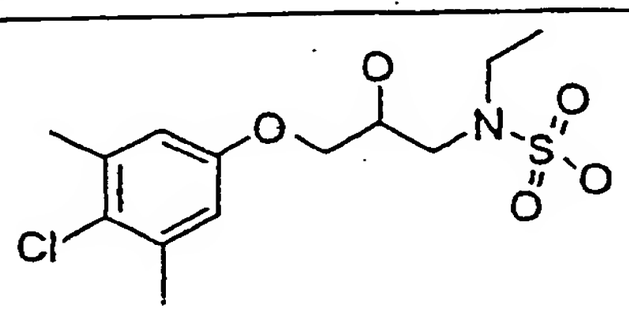
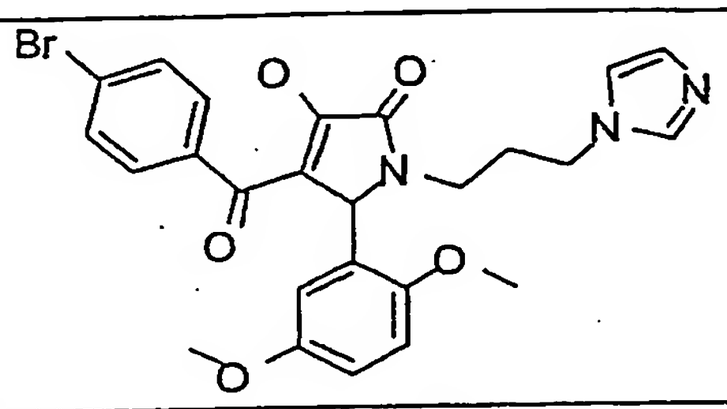
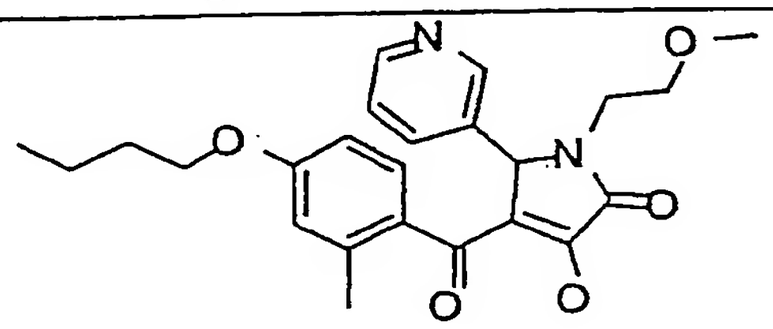
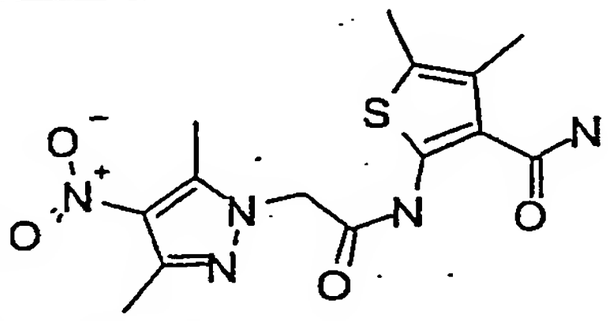
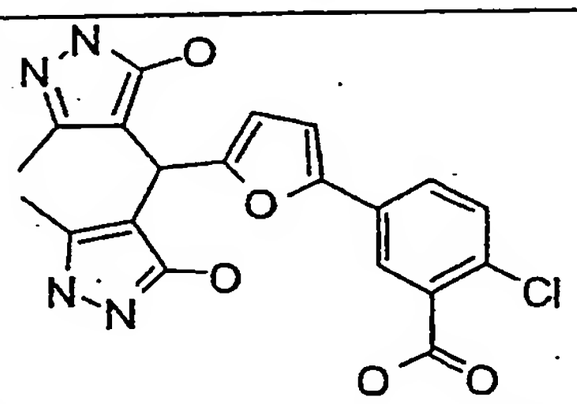
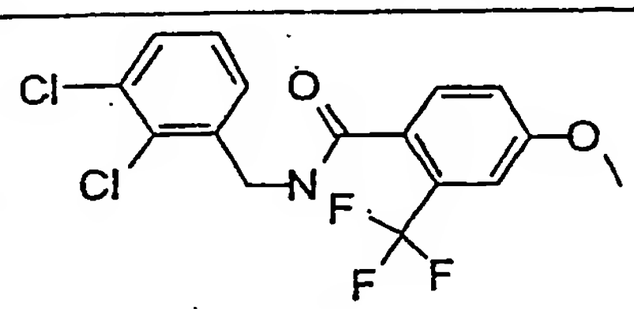
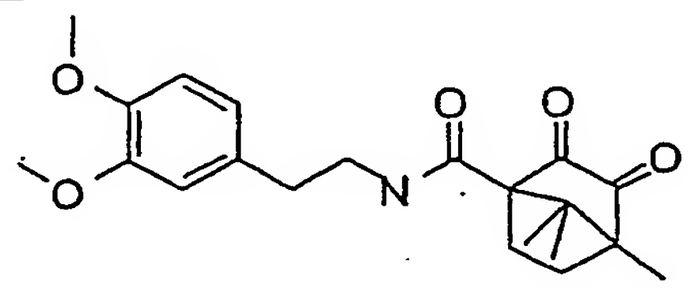
2. The use according to claim 1 for the prevention and/or treatment of inflammation-induced and/or immune-mediated loss of bone and/or cartilage in a mammal.

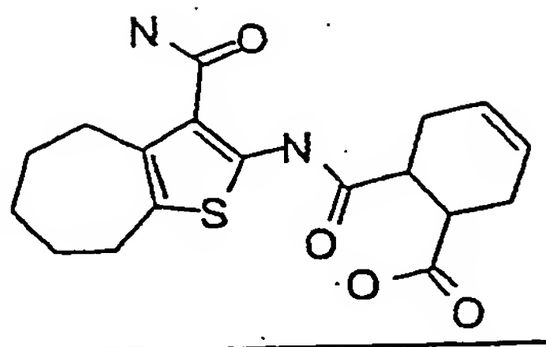
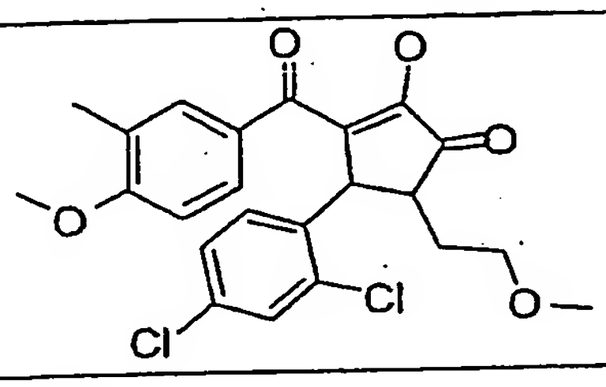
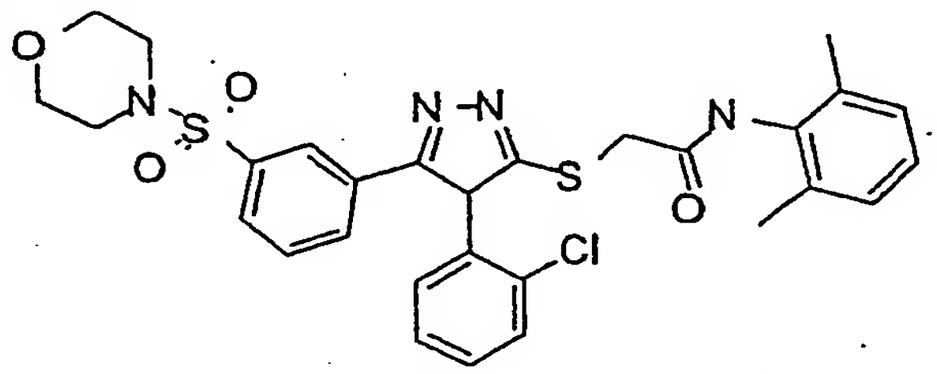
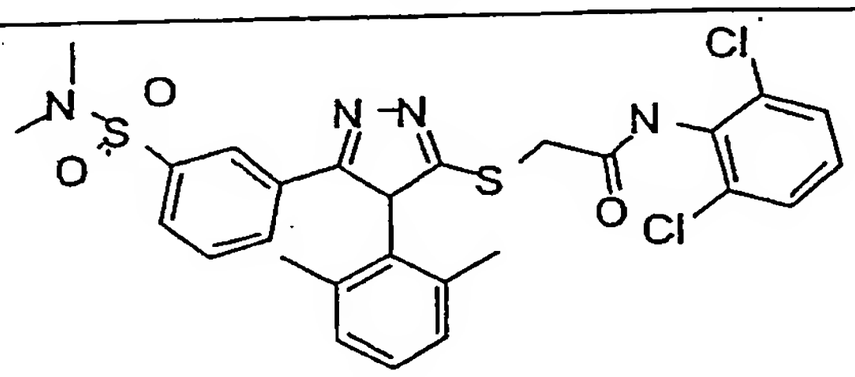
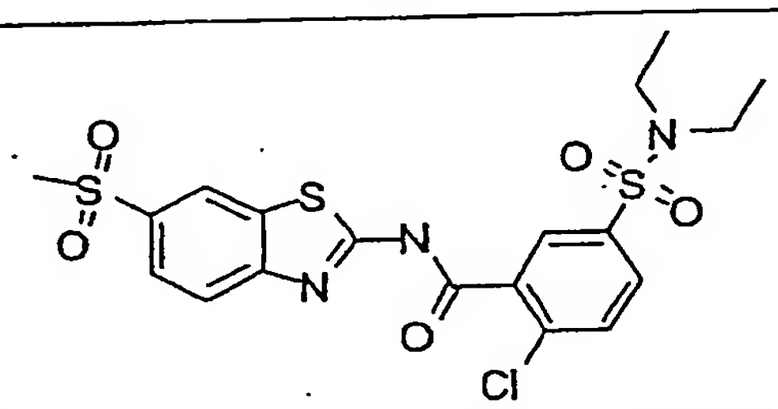
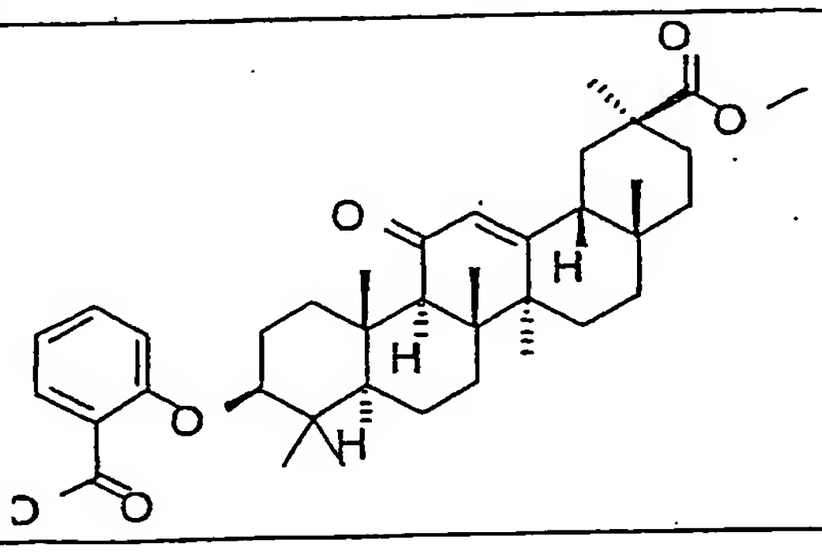
3. The use according to claim 2, wherein the mammal is a human.

4. The use according to claim 1, wherein said use is for the prevention and/or treatment of periodontitis and/or arthritis selected from the group consisting of osteoarthritis and/or rheumatoid arthritis.

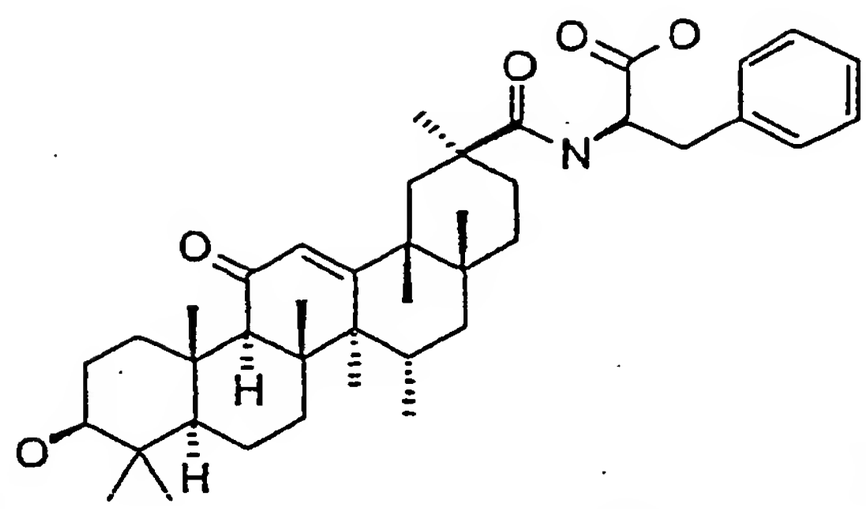
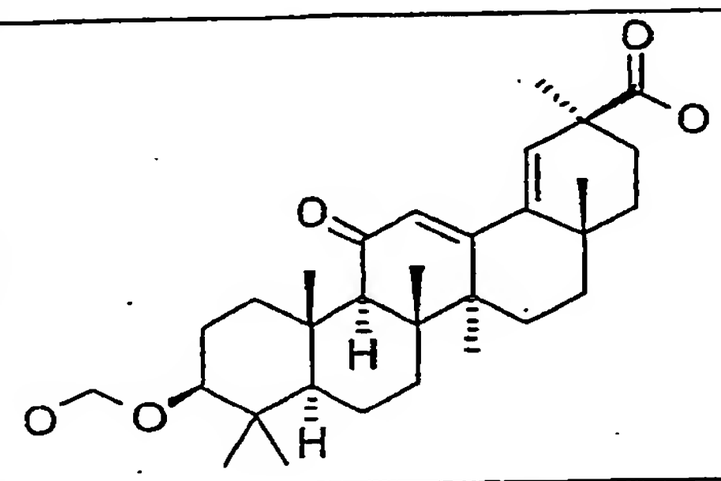
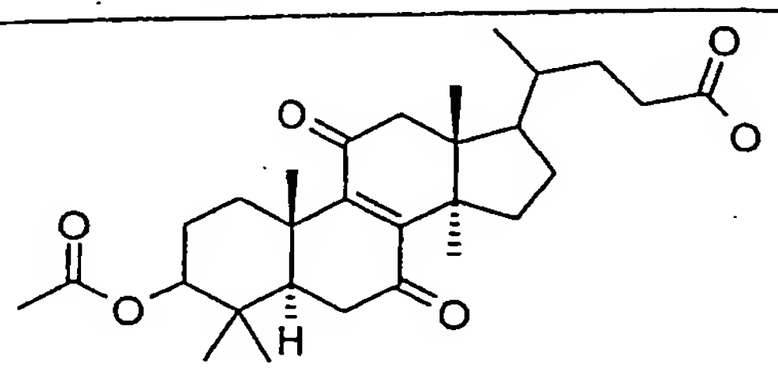
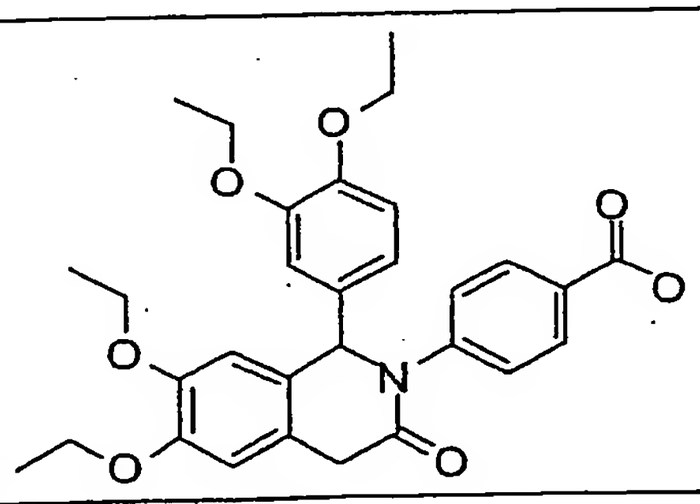
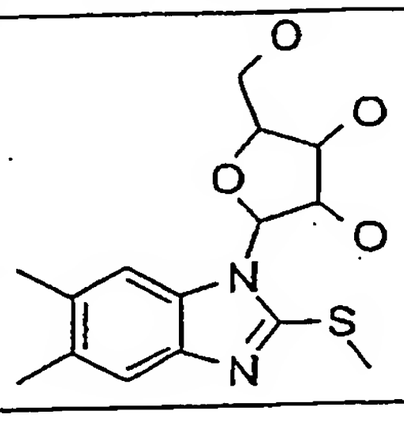
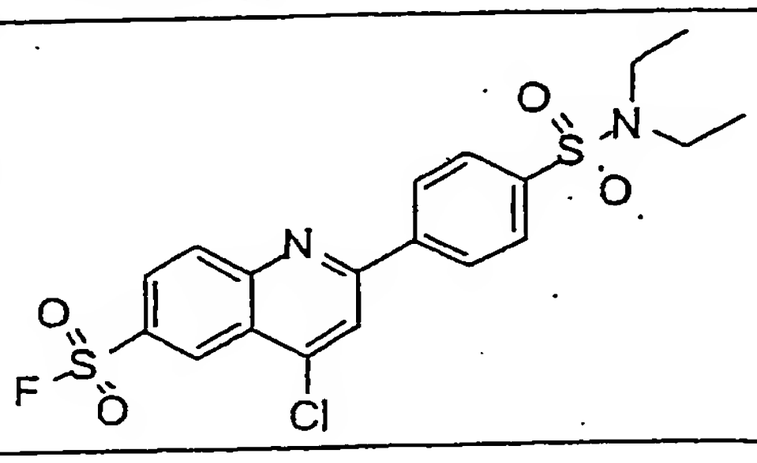
5. The use according to any one of claims 1 to 4, wherein the 11- β-HSD-type 1 and/or type 2 inhibitor is 18-β-glycyrrhetinic acid.

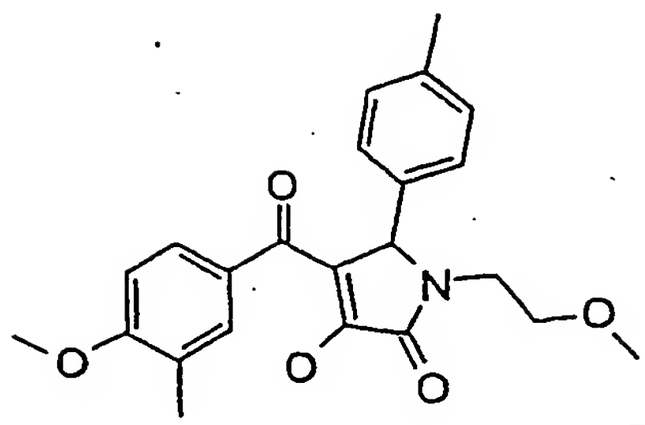
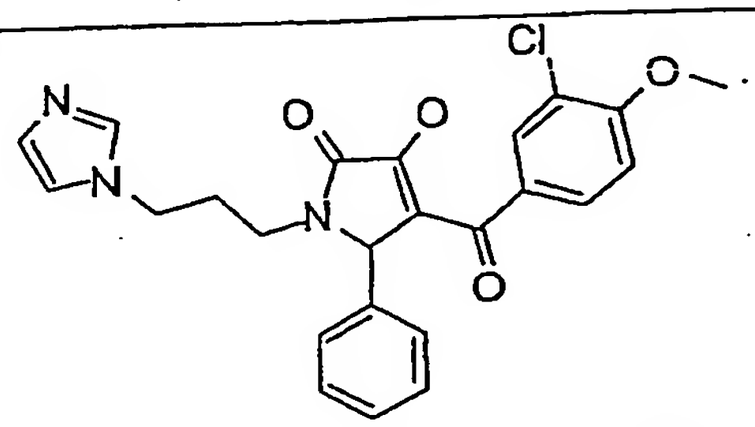
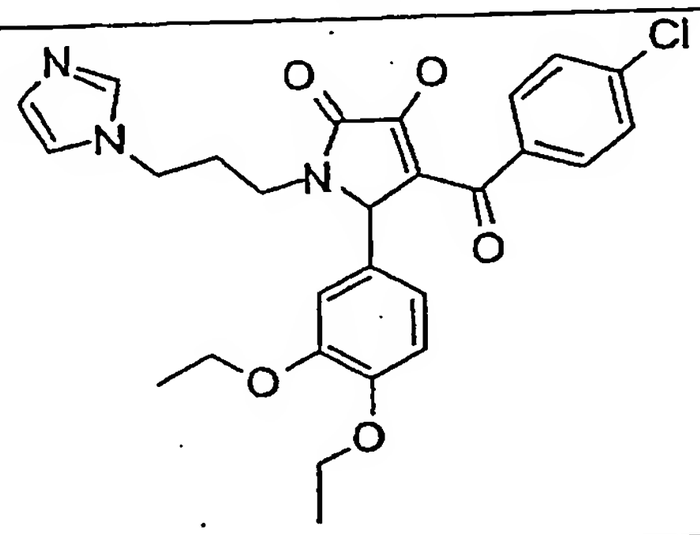
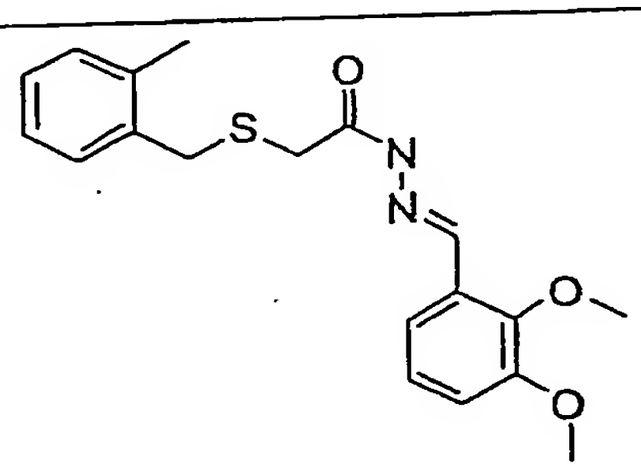
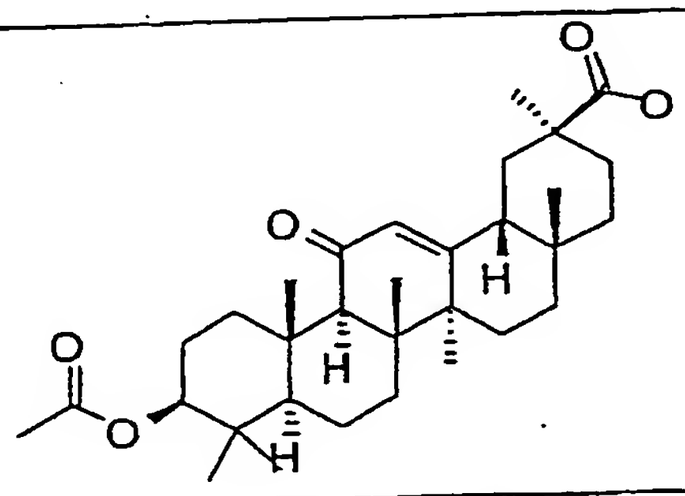
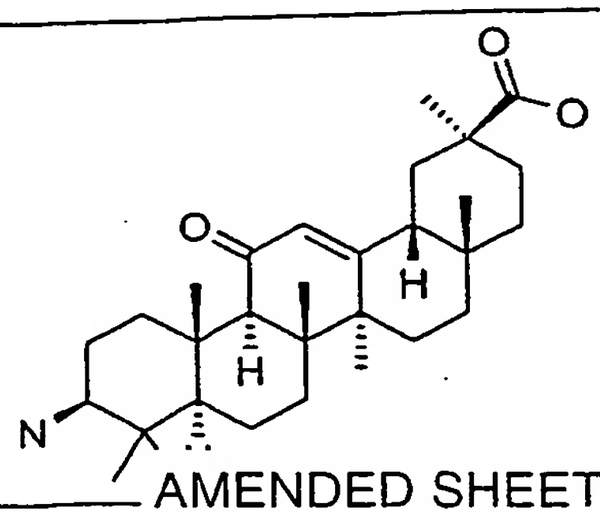
6. The use according to any one of claims 1 to 4, wherein the 11-β-HSD-type 1 and/or type 2 inhibitor is selected from the group consisting of the following formulas:

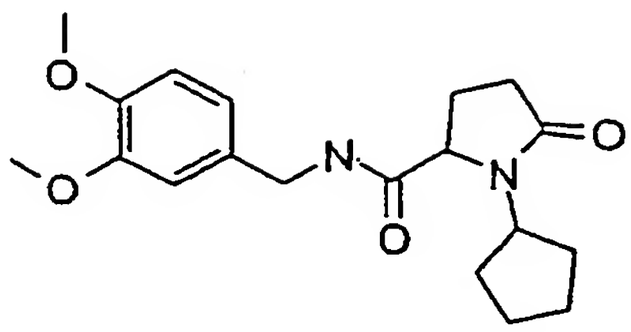
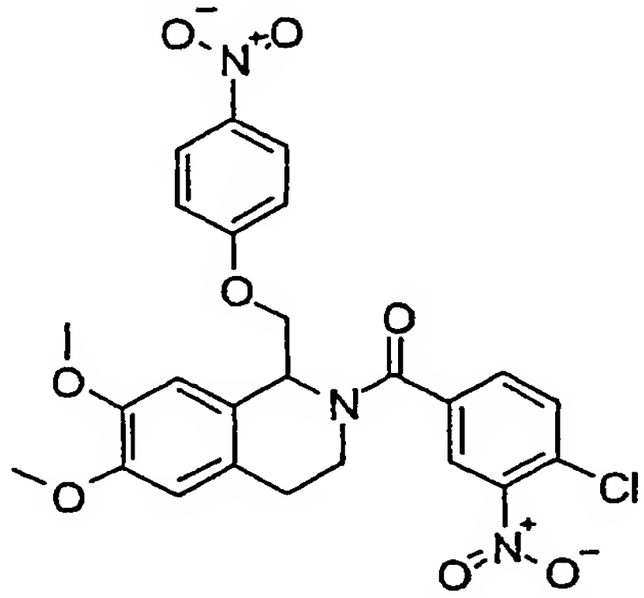
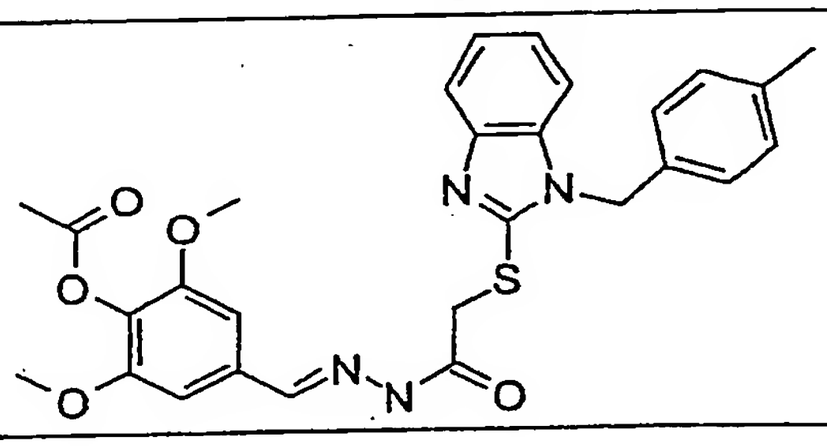
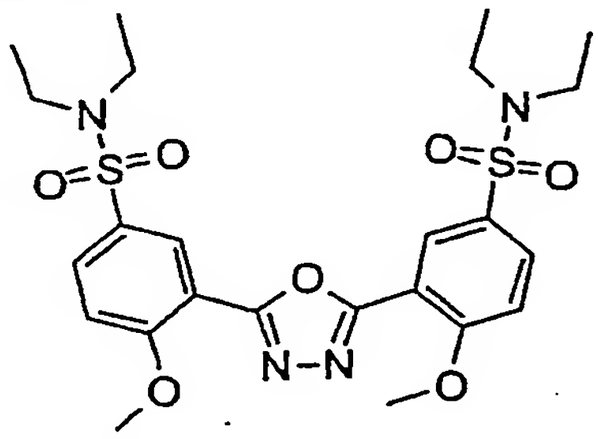
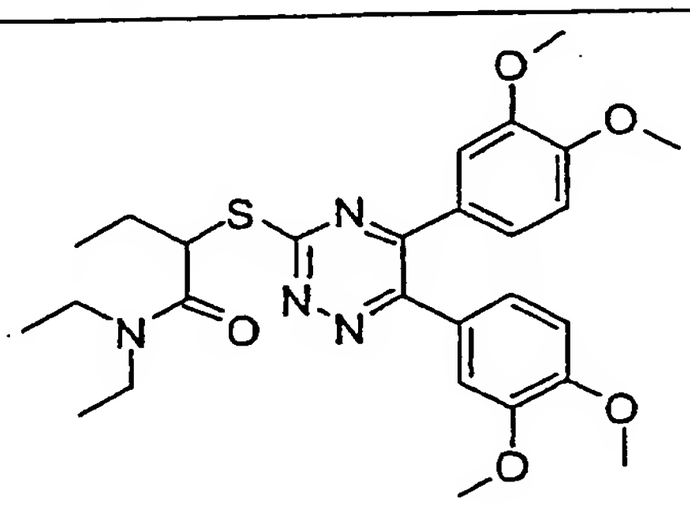
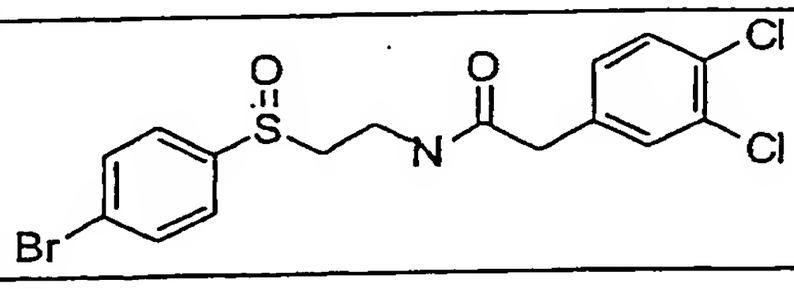
Compound Name	Structure
Formula 1	
Formula 2	
Formula 3	
Formula 4	
Formula 5	
Formula 6	
Formula 7	

Formula 8	
Formula 9	
Formula 10	
Formula 11	
Formula 12	
Formula 13	

AMENDED SHEET

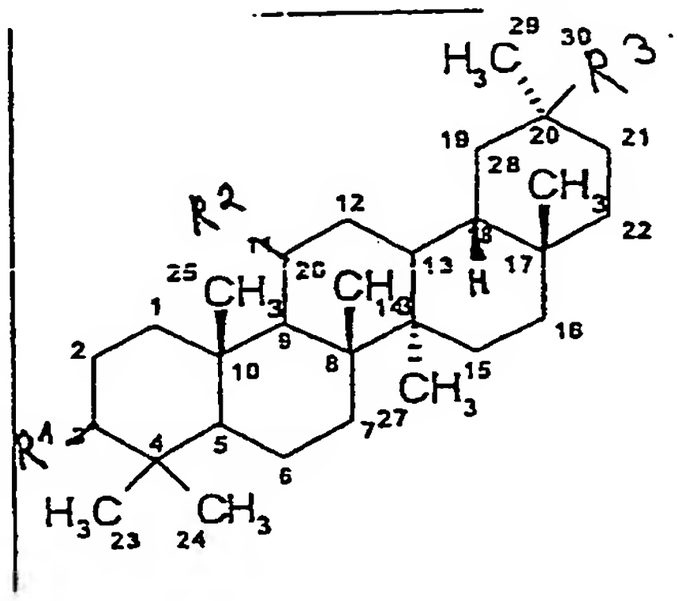
Formula 14	
Formula 15	
Formula 16	
Formula 17	
Formula 18	
Formula 19	

Formula 20	
Formula 21	
Formula 22	
Formula 23	
Formula 24	
Formula 25	

Formula 26	
Formula 27	
Formula 28	
Formula 29	
Formula 30	
Formula 31	

AMENDED SHEET

7. The use according to any one of claims 1-4, wherein the 11-β-HSD-type 1 and/or type 2 inhibitor has the structure of formula I:



formula I

wherein R^1 is

a hydrogen,

a linear or branched C_1-C_{10} alkyl group,

a linear or branched C_1-C_{10} alkenyl group,

a linear or branched C_1-C_{10} alkynyl group,

an ester, amino, halo, hydroxy, carbonyl, carboxy, carboxyphenoxy, C_1-C_4 alkoxy, C_1-C_4 alkoxy carbonyl, C_1-C_4 alkyl amino, di-(C_1-C_4-alkyl)amino, cyano, carboxy amide, carboxy-(C_1-C_4-alkyl)amino, carboxy-di(C_1-C_4-alkyl)sulfo, sulfido (C_1-C_4-alkyl), sulfoxido (C_1-C_4-alkyl), sulfono (C_1-C_4-aminoalkyl) or thio group, a saturated or unsaturated, aromatic or heteroaromatic mono- or polycyclic group,

wherein said cyclic group may be mono- or polysubstituted with an ester, amino, halo, hydroxy, C_1-C_4 alkoxy, carboxy, carbonyl, C_1-C_4 alkoxycarbonyl, carboxyphenoxy, C_1-C_4 alkyl amino, di-(C_1-C_4-alkyl)amino, cyano, carboxy amide, carboxy-(C_1-C_4-alkyl)amino, carboxy-di(C_1-C_4-alkyl)amino, sulfo, sulfido (C_1-C_4-alkyl), sulfoxido (C_1-C_4-alkyl), sulfono (C_1-C_4-alkyl), thio, C_1-C_4 alkyl, C_2-C_4 alkenyl or C_2-C_4 alkynyl group;

R^2 is

a hydrogen, C_1-C_4 alkyl, carbonyl, ester, amino, halo, carbonyl, hydroxy, carboxy, carboxyphenoxy, C_1-C_4 alkoxy, C_1-C_4 alkoxy carbonyl, C_1-C_4 alkyl amino, di-(C_1-C_4-alkyl)amino, cyano, carboxy amide, carboxy-(C_1-C_4-alkyl)

amino, carboxy-di(C_1-C_4-alkyl), sulfo, sulfido (C_1-C_4-alkyl), sulfoxido (C_1-C_4-alkyl), sulfono (C_1-C_4-alkyl) or thio group;

R^3 is

a hydrogen,

a linear or branched C_1-C_{10} alkyl group,

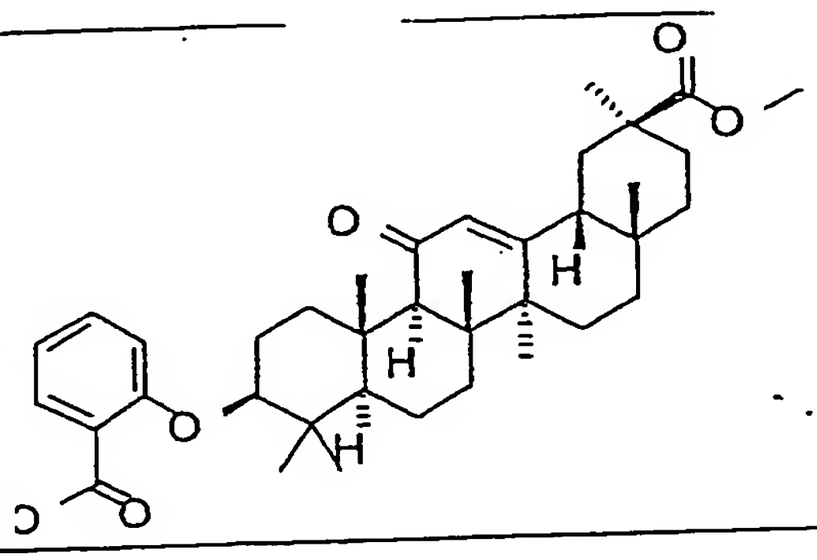
a linear or branched C_1-C_{10} alkenyl group,

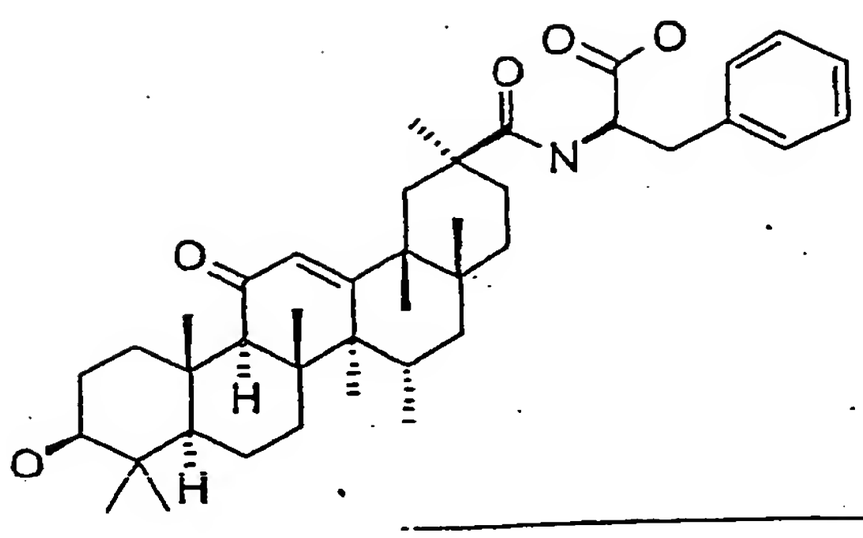
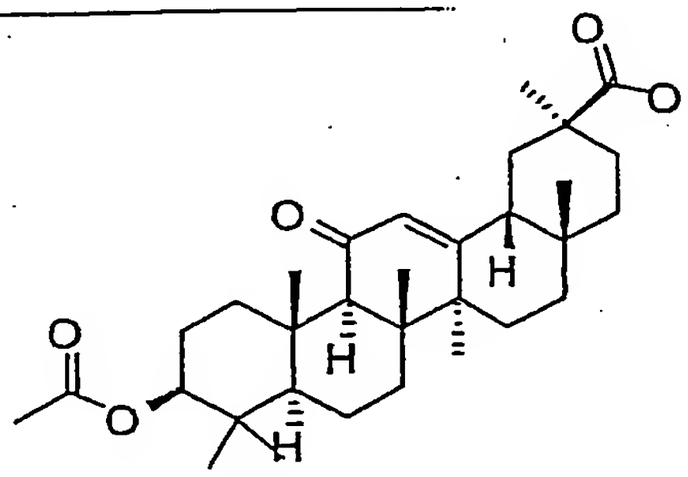
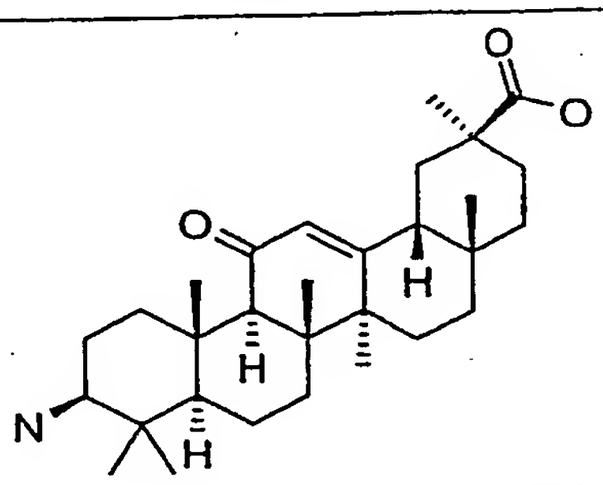
a linear or branched C_1-C_{10} alkynyl group,

an ester, amino, halo, hydroxy, carbonyl, carboxy, carboxyphenoxy, C_1-C_4 alkoxy, C_1-C_4 alkoxy carbonyl, C_1-C_4 alkyl amino, di-(C_1-C_4-alkyl)amino, cyano, carboxy amide, carboxy-(C_1-C_4-alkyl)amino, carboxy-di(C_1-C_4-alkyl)sulfo, sulfido (C_1-C_4-alkyl), sulfoxido (C_1-C_4-alkyl), sulfono (C_1-C_4-aminoalkyl) or thio group, a saturated or unsaturated, aromatic or heteroaromatic mono- or polycyclic group;

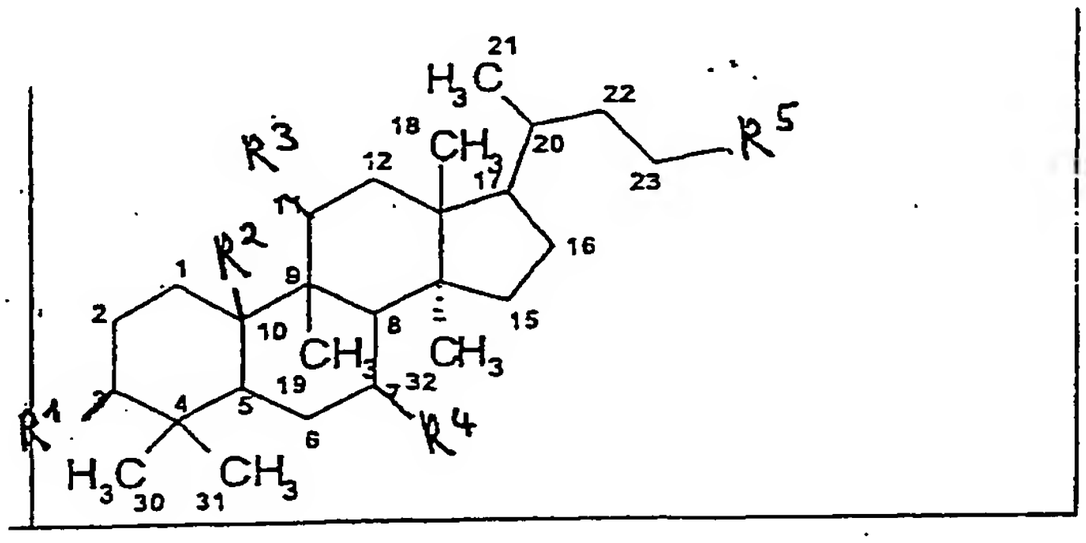
wherein the chemical bond from carbon 13 to 14 is saturated or unsaturated;
or a salt or derivative thereof in the form of an individual enantiomer, diastereomer or a mixture thereof.

8. The use according to claim 1, wherein the 11-β-HSD-type 1 and/or type 2 inhibitor is selected from the group consisting of the following formulas:

Formula 13	

Formula 14	
Formula 24	
Formula 25	

9. The use according to any one of claims 1-4, wherein the 11-β-HSD-type 1 and/or type 2 inhibitor has the structure of formula II:



formula II

wherein R^1 is

a hydrogen,

a linear or branched C_1-C_{10} alkyl group,

a linear or branched C_1-C_{10} alkenyl group,

a linear or branched C_1-C_{10} alkynyl group,

an ester, amino, halo, hydroxy, carbonyl, carboxy, carboxyphenoxy, C_1-C_4 alkoxy, C_1-C_4 alkoxy carbonyl, C_1-C_4 alkyl amino, di-(C_1-C_4-alkyl)amino, cyano, carboxy amide, carboxy-(C_1-C_4-alkyl)amino, carboxy-di(C_1-C_4-alkyl)sulfo, sulfido (C_1-C_4-alkyl), sulfoxido (C_1-C_4-alkyl), sulfono (C_1-C_4-aminoalkyl), thio group, a saturated or unsaturated, aromatic or heteroaromatic mono- or polycyclic group,

wherein said cyclic group may be mono- or polysubstituted with an ester, amino, halo, hydroxy, C_1-C_4 alkoxy, carbonyl, carboxy, C_1-C_4 alkoxycarbonyl, carboxyphenoxy, C_1-C_4 alkyl amino, di-(C_1-C_4-alkyl)amino, cyano, carboxy amide, carboxy-(C_1-C_4-alkyl)amino, carboxy-di(C_1-C_4-alkyl)amino, sulfo, sulfido (C_1-C_4-alkyl), sulfoxido (C_1-C_4-alkyl), sulfono (C_1-C_4-alkyl), thio, C_1-C_4 alkyl, C_2-C_4 alkenyl or C_2-C_4 alkynyl group;

R^2 is a hydrogen or C_1-C_4 alkyl,

R^3 and R^4 are each selected from

a hydrogen

a linear or branched C_1-C_{10} alkyl group,

a linear or branched C_1-C_{10} alkenyl group,

a linear or branched C_1-C_{10} alkynyl group,

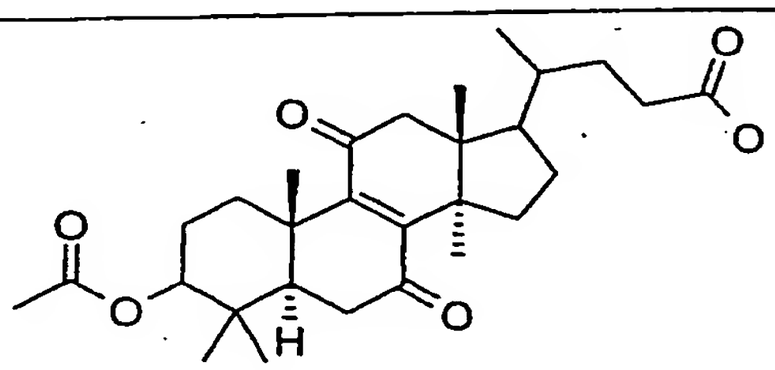
an ester, amino, halo, hydroxy, carbonyl, carboxy, carboxyphenoxy, C_1-C_4 alkoxy, C_1-C_4 alkoxy carbonyl, C_1-C_4 alkyl amino, di-(C_1-C_4-alkyl)amino, cyano, carboxy amide, carboxy-(C_1-C_4-alkyl)amino, carboxy-di(C_1-C_4-alkyl)sulfo, sulfido (C_1-C_4-alkyl), sulfoxido (C_1-C_4-alkyl), sulfono (C_1-C_4-aminoalkyl), thio group, a saturated or unsaturated, aromatic or heteroaromatic mono- or polycyclic group;

R^5 is a hydrogen, C_1-C_4 alky, carbonyl, ester, amino, halo, hydroxy, carboxy, carboxyphenoxy, C_1-C_4 alkoxy, C_1-C_4 alkoxy carbonyl, C_1-C_4 alkyl amino, di-(C_1-C_4-alkyl)amino, cyano, carboxy amide, carboxy-(C_1-C_4-alkyl) amino, carboxy-di(C_1-C_4-alkyl), sulfo, sulfido (C_1-C_4-alkyl), sulfoxido (C_1-

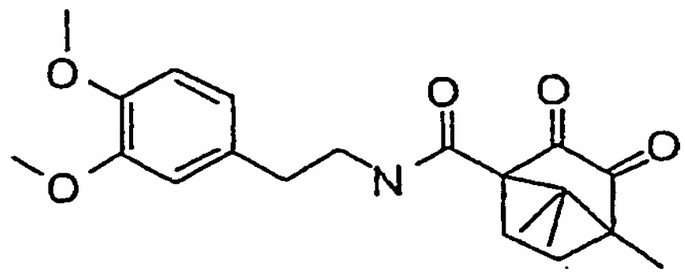
C_4-alkyl), sulfono (C_1-C_4-alkyl) or thio group,

wherein the chemical bond from carbon 8 to 9 is saturated or unsaturated;
wherein the chemical bond from carbon 13 to 14 is saturated or unsaturated;
or a salt or derivative thereof in the form of an individual enantiomer, diastereomer or a mixture thereof.

10. The use according to claim 1, wherein the 11-β-HSD-type 1 and/or type 2 inhibitor is:

Formula 16	

11. The use according to claim 6, wherein the 11-β-HSD-type 1 and/or type 2 inhibitor is:

Formula 7	

12. The use of any one of claims 1 to 11, wherein the pharmaceutical agent comprises at least one 11-β-HSD-type 1 and/or type 2 inhibitor in combination with at least one active ingredient being effective in the

prevention and/or treatment of inflammation-induced and/or immune-mediated loss of bone and/or cartilage.

13. The use according to any one of claims 1 to 12, wherein the pharmaceutical agent is administered in a dose of 5 to 100 mg/kg body weight per day.

14. The use of any one of claims 1 to 13, wherein the pharmaceutical agent is administered orally, sublingually, intravenously, intramuscularly, intraarticularly, intraarterially, intramedullarily, intrathecally, intraventricularly, intraocularly, intracerebrally, intracranially, respiratorally, intratracheally, nasopharyngeally, transdermally, intradermally, subcutaneously, intraperitoneally, intranasally, enterally, topically, via rectal means, via infusion and/or via implant.

15. The use according to claim 14, wherein the pharmaceutical agent is administed orally.